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Long term macrolide antibiotics for the treatment of bronchiectasis in adults - individual participant data meta-analysis

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-Evidence before this study:

Data sources and searches

Two investigators searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Web of Science using the search strategy described in the online supplement. Searches were conducted from 2000 to 30th September 2018. No language restrictions were applied. Searches were supplemented with review of reference lists and by reviewing previous meta-analyses and guidelines. Clearly ineligible studies were excluded based on abstract review alone.

We identified 266 references and after exclusion of non-relevant studies we identified 3 randomized controlled trials comparing long term treatment with macrolide antibiotics (>3 months duration) compared with placebo where the primary outcome was the reduction of exacerbations. We identified several existing aggregate meta-analyses that suggested that macrolides reduce the frequency of exacerbations of bronchiectasis. Neither the individual trials nor the existing meta-analyses reported on the effectiveness of macrolides in different subpopulations. Identifying which patients benefit from macrolides was identified as a key research priority in bronchiectasis. The current European Respiratory Society guidelines suggest consideration of macrolides for patients without *Pseudomonas aeruginosa* infection with a history of at least 3 exacerbations in the previous year.

Added value of this study:

We report the first individual patient data meta-analysis of long term macrolide therapy in bronchiectasis. Our data from 341 patients enrolled in randomized clinical trials in the Netherlands, New Zealand and Australia suggests that macrolide treatment compared to placebo for 6-12 months results in a 50% reduction in the frequency of exacerbations. Additional benefits included prolongation of the time to first exacerbation and statistically significant improvements in quality of life measured by the St Georges Respiratory Questionnaire. Lung function was not significantly improved. Analyses in pre-specified subgroups including age, sex, disease severity and baseline microbiology suggested that macrolides effectively reduced exacerbations across all subgroups of patients. Importantly, macrolides

had a significant and clinically meaningful impact in patients where macrolide are not currently considered as first line treatment, including patients with *P. aeruginosa* infection and patients with less than 3 exacerbations per year.

Implications of all the available evidence:

Our data suggests that macrolide therapy is highly effective in reducing the frequency of exacerbations in bronchiectasis. Given the strong evidence that exacerbations contribute to long term morbidity and mortality in bronchiectasis macrolides should be considered in patients with frequent or severe exacerbations. Current bronchiectasis guidelines recommend inhaled antibiotics as first line treatment for patients with *P. aeruginosa* infection and frequent exacerbations. In view of the high level of effectiveness in reducing exacerbations demonstrated by macrolides in the *P. aeruginosa* subgroup, and recent equivocal data on the effectiveness of inhaled antibiotics, macrolides may be considered as first line for patients with *P. aeruginosa* infection. The magnitude of benefit was similar in patients with 1-2 exacerbations per year as in the subgroup with 3 exacerbations per year, in whom macrolides are recommended by international guidelines, suggesting an individualised discussion of the risks and benefits of macrolides. Macrolides have important adverse events and the potential to induce antimicrobial resistance and so should be used judiciously. No studies were identified with a treatment duration of more than 1 year and so the longer term efficacy and safety of macrolides is unknown.

Summary

Background: Bronchiectasis guidelines recommend long term macrolide treatment for patients with 3 or more exacerbations per year without *P.* aeruginosa infection. Randomized controlled trials (RCTs) suggest that long term macrolide treatment can prevent exacerbations in adult patients with bronchiectasis but these individual studies have been too small to conduct meaningful subgroup analyses. Individual patient data (IPD) meta-analysis could explore macrolide benefit in subpopulations including those where macrolide therapy is not currently recommended.

Methods: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and Web of Science were searched to identify randomized controlled trials of macrolide antibiotics for at least 3 months with a primary outcome of bronchiectasis exacerbations. IPD meta-analysis was performed using fixed effects models adjusting for age, sex, FEV_1 and trial.

Findings: IPD was obtained for 341 participants in 3 RCTs. Macrolide antibiotics reduced the frequency of exacerbations adjusted incidence rate ratio (IRR) 0.49 95% CI 0.36-0.66,p<0.0001, improved the time to first exacerbation, (hazard ratio 0.46 95% CI 0.34-0.61,p<0.0001) and were associated with improved quality of life measured by the St Georges Respiratory Questionnaire (mean improvement 2.9 points (95% CI 0.03 to 5.8,p=0.048). Pre-specified subgroup analyses revealed a reduced frequency of exacerbations in all pre-specified subgroups including a high level of benefit in patients with *Pseudomonas aeruginosa* infection (IRR 0.36 95% CI 0.18-0.72,p=0.004) and in patients with less than 3 exacerbations per year (IRR 0.37 95% CI 0.16-0.88,p=0.02).

Interpretation: Long-term macrolide treatment significantly reduces the rate of exacerbations in patients with bronchiectasis with similar benefits observed in all subgroups based on patient characteristics.

Background

Bronchiectasis is a common chronic disease associated with frequent respiratory tract infections, chronic symptoms of cough and sputum production.[1] The disease has a devastating impact on patients' quality of life.[2] In addition exacerbations of bronchiectasis, which are characterised by increases in symptoms requiring antibiotic treatment, are a major driver of disease progression and associated mortality.[3,4]

Bronchiectasis is characterised by a "vicious vortex" of bacterial infection, airway inflammation and impaired mucociliary clearance which each interact to promote lung damage.[5,6] There are few evidence based treatments for bronchiectasis as reflected in the recent European Respiratory Society bronchiectasis management guidelines which were unable to recommend any pharmacotherapy with a high quality of evidence.[7] Macrolide antibiotics are among the most widely used chronic treatments to prevent exacerbations in bronchiectasis.[8,9] They are particularly attractive because there is evidence they target each of the key components of bronchiectasis pathophysiology. In addition to reducing bacterial burden, they have well established immunomodulatory effects which include suppression of neutrophil mediated lung damage, and they also enhance cilia function to promote mucociliary clearance.[10-12]

A number of randomized controlled trials have demonstrated that the macrolide class of antibiotics significantly reduces exacerbations in bronchiectasis. [13-16] Meta-analysis of these trials based on aggregate data suggest a clear reduction in the frequency of exacerbations with macrolide therapy along with other benefits. For example the meta-analysis of Gao et al identified 9 trials with 559 participants of which 6 were conducted in adults.[17,18] Macrolide therapy reduced the frequency of exacerbations by 58%, and reduced the proportion of patients experiencing exacerbations with slight improvements in FEV_1 and quality of life.[17] Macrolides, however, were associated with increased adverse events such as diarrhoea and abdominal discomfort and also with an increased risk of antibiotic resistance.[9,13] Hearing loss and cardiovascular effects have been detected in other patient populations but were not observed in bronchiectasis trials.[9,19,20] Based on this, the most recent Cochrane review called for further research to identify specific patient groups who are most responsive to macrolides.[21] An ERS/EMBARC consensus statement, based on a survey of over 100 bronchiectasis experts and over 1000 patients, published in 2016 identified "further studies to define the optimal patient population to benefit from long-term macrolide therapy" as one of the 22 key research priorities in bronchiectasis.[22]

We therefore undertook an individual participant data (IPD) meta-analysis of studies of long-term macrolides in adults with the objective of identifying responsive patient subgroups.

Methods

We performed a systematic review and one-step and two-step meta-analysis of individual participant data. The review protocol was prospectively registered with the PROSPERO international register of systematic reviews- registration number CRD42018102908. Systematic review and meta-analyses are exempt from research ethics committee review in the UK. Findings are reported according to the PRISMA guidelines for IPD meta-analysis.[23]

Study selection

Double blind placebo-controlled randomized controlled trials of macrolide antibiotics in adult patients with bronchiectasis were eligible for inclusion if they also fulfilled the following criteria: long term treatment, defined a-priori as treatment for at least 3 months based on the previous ERS guidelines and recording of exacerbation rate as a primary or secondary outcome.[7] Studies in patients with cystic fibrosis bronchiectasis were excluded.

Data sources and searches

Two investigators (JDC and MLC) searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Web of Science using the search strategy described in the online supplement. Searches were conducted from 2000 to 30th September 2018. No language restrictions were applied. Searches were supplemented with review of reference lists and by reviewing previous meta-analyses and guidelines. Clearly ineligible studies were excluded based on abstract review alone.

Definition of outcomes

The primary outcome of the meta-analysis was the frequency of exacerbations requiring treatment with antibiotics. This was selected based on clinical and regulatory opinion that this is the most important clinical endpoint in bronchiectasis studies.[4,24,25] Exacerbation definitions varied across different studies and therefore a-priori definitions were used based on prescription of antibiotics for an increase in respiratory symptoms. Secondary endpoints were time to the first exacerbation, the proportion of

patients experiencing an exacerbation, change in quality of life using the St.Georges Respiratory Questionnaire (SGRQ) and change in forced expiratory volume in 1 second (FEV_1) in millilitres.

Data synthesis and analysis

Our IPD meta-analysis approach utilised published guidelines.[26] Initially, all studies were re-analysed separately to replicate the results of the original reported studies, using the methodology described in the respective publications. Any discrepancies were resolved with the original study authors. We then performed a one-step and two-step meta-analysis of the primary outcome, exacerbation frequency. This was analysed using a negative binomial model with time in study as an offset. Results were expressed as incident rate ratios (IRRs) with associated 95% confidence intervals (95% CI). For secondary outcomes we performed one-step meta-analysis only. In the one-step analysis approaches, IPD from studies were modelled with fixed effects adjusting for age, sex, FEV_1 at baseline and trial to obtain the pooled intervention effect estimate. Adjustment for trial as a fixed effect was pre-specified following literature review based on the very similar inclusion criteria, patient characteristics, design and outcomes used in all three studies ultimately included in the meta-analysis. A sensitivity analysis for the primary outcome was performed controlling for study as a random effect. To check the validity of the confidence intervals around the estimates a non-parametric bootstrap was performed. Time to next exacerbation was analysed using Cox proportional hazards regression adjusted for age, sex and FEV_1 at baseline as covariates and with study as a stratification variable. The proportional hazards assumption was confirmed by inspection of log minus log plots. Continuous outcomes were analysed using a generalized linear model with the addition of baseline value of the endpoint as an additional covariate. In addition to the analysis of quality of life as a continuous outcome variable we performed a responder analysis using logistic regression with the response being an improvement of 4 points or more in the SGRQ score, the reported minimum clinically important difference for this score.[24,25] For the two-step approach to the primary outcome the individual participant data was analysed using a negative binomial regression with adjustment for age, sex and baseline FEV_1 to produce an estimate of treatment effect for each study. Meta-analysis was then performed using the Mantel-Haenszel method, and heterogeneity was reported using the I^2 statistic. Analyses were performed using R version 3.4.0 and Statistical Package for the Social Sciences (SPSS) version 22. The two step meta-analysis was performed using Review Manager 5 (Cochrane Collaboration).

Subgroup analyses

A key objective of this study was to identify subgroups of patients in which macrolides had a differential effect. Interactions were evaluated by including interactions terms in the appropriate models as described above. Pre-specified subgroup analyses were conducted for each of the primary and secondary endpoints using one-step meta-analysis only. Subgroups were defined as follows

Age groups <50 years, 50-69 years and ≥70 years; sex (male and female); prior exacerbation frequency (1-2 per year, 3 per year and ≥4 per year); smoking status (never and ex or current smoker); inhaled corticosteroid use as baseline; body mass index at baseline (<21, 21-24.9, 25-29.9 and ≥30); aetiology (idiopathic and post-infective aetiology and other aetiologies); C-reactive protein at baseline (<2mg/L, 2-5mg/L, 5.1-10mg/L and >10mg/L); Baseline FEV_1 % predicted (>80%, 50-79%, <50%); SGRQ total score (<30, 30-49, ≥50); *Pseudomonas aeruginosa* in sputum culture at baseline. Statistical significance was inferred for subgroup effects in which the p-value for interaction was less than 0.05.

Role of the funding source

All funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study inclusion and individual participant data

Figure 1 shows the selection of studies for analysis. Two hundred and thirty four potentially eligible studies were identified. After exclusion of 231 manuscripts that did not meet the inclusion criteria, 3 double blind randomized placebo controlled trials with 341 participants were included. We sought IPD for these 3 trials and obtained data for all eligible participants.

Study and participant characteristics

The three included RCTs were conducted in the Netherlands, New Zealand and Australia. Two trials compared azithromycin vs placebo while one trial compared erythromycin vs placebo. Randomized participants were aged 18 to 80 years and 222/341 (65.1%) patients were female. Study and participant characteristics are shown in table 1. The final analysis included 173 patients treated with macrolide and 168 patients treated with placebo.

Risk of bias

Details of the risk of bias assessment are shown in appendix table E1. All RCTs contributing data to the IPD meta-analysis were assessed as being at low risk of bias.

Primary outcome- frequency of exacerbations

In the one step meta-analysis long term macrolide therapy was associated with a marked reduction in frequency of exacerbations (IRR 0.49 95% CI 0.36-0.66,$p<0.0001$). Sensitivity analyses were performed excluding the adjustment for baseline covariates and not including the offset which identified similar results (Table E2). Likewise, controlling for study as a random effect did not impact on the overall conclusions. A non-parametric bootstrap of the data produced similar confidence intervals to those obtained directly from the model.

The two step meta-analysis identified a similar result to the one step approach, IRR 0.51 (0.37-0.69,$p<0.0001$) with no heterogeneity, $I^2=0\%$ (figure E1).

Results of subgroup analyses for frequency of exacerbations

The results of the subgroup analyses based on patient characteristics are shown in table 2. None of the subgroup analyses showed statistically significant interactions with the exception of aetiology.

Non-significant trends suggested improved response with increasing age, extremes of BMI and increasing systematic inflammation. Patients with *P. aeruginosa* also showed a statistically significant response to macrolide treatment, (IRR 0.36 95% CI 0.18-0.72,p=0.004). Response showed no significant interaction based on sputum culture. *H. influenzae* was the second most frequent pathogen and this subgroup showed no differential response, (IRR 0.40 95%CI 0.10-1.69,p=0.21). No significant difference was observed in the IRR between different strata of baseline exacerbation frequency. Absolute risk reductions in each strata are shown in table E3 online. The event based number needed to treat was calculated as 1.0 for patients with 4 or more exacerbations per year, 1.7 for patients with 3 exacerbations in the previous year and 1.5 for patients with a history of 1-2 exacerbations per year in the prior year.

Secondary outcomes- time to first exacerbation

Time to first exacerbation was significantly prolonged with macrolide treatment, adjusted hazard ratio 0.46 95% CI 0.34-0.61,p<0.0001. The model derived median times to first exacerbation were 98 days in the placebo groups and 280 days in the macrolide treated groups. Table 3 shows time to first exacerbation in the pre-specified subgroups.

Secondary outcomes- St Georges Respiratory Questionnaire

We identified a statistically significant improvement in quality of life with macrolide treatment vs placebo of 2.93 points (95% CI 0.03 to 5.83,p=0.048). The number of patients achieving a greater than 4 point improvement in SGRQ was also increased with macrolide therapy, Odds ratio 1.61 (95% CI 1.02-2.54,p=0.042). The strongest relationships with improvement in symptoms were observed when comparing those with idiopathic/post-infective aetiology against other aetiologies, where the interaction was statistically significant. Non-significant trends towards greater QoL improvement were seen in older patients, females, ex-smokers, inhaled corticosteroid users, and patients with BMI >30mg/k^2 (figure 2, Table E4).

Secondary outcomes: FEV_1 change from baseline

Macrolides were not associated with a significant improvement in FEV_1, however a non-significant improvement of 67ml at 1 year was observed (95% CI -22m to 112ml, p=0.14). The subgroup effects on lung function are shown in figure 3. Only the interaction between idiopathic/postinfective aetiology and other aetiologies was significant at p=0.03. The highest responses were seen in inhaled corticosteroid users, aetiologies other than idiopathic/postinfective, higher systemic inflammation and *P. aeruginosa* at baseline (Figure 3, Table E4).

Discussion

This IPD meta-analysis has demonstrated that macrolides reduce the frequency of exacerbations by 51% over 6-12 months and are associated with a significant improvement in quality of life measured using the SGRQ. The mean improvement in quality of life did not exceed the minimum clinically important difference but the proportion of patients achieving a clinically meaningful improvement in quality of life was increased with macrolide vs placebo. The findings of this study agree with the findings of the original BAT, BLESS and EMBRACE studies and the results of prior meta-analyses.[13-15,17,21] The advantage of IPD meta-analysis is the ability to standardise the analysis and reporting of each trial. Previous meta-analyses have been limited in their assessment of frequency of exacerbations, time to first exacerbation, and quality of life and other endpoints because of different methods of reporting in the 3 studies we reviewed. The most recent Cochrane systematic review of macrolide antibiotics in bronchiectasis could not fully analyse the frequency endpoint due to heterogeneous reporting of data and therefore limited exacerbation analysis to the proportion of patients experiencing one or more exacerbations.[21] Previous estimates of the effect of quality of life and lung function were also based on incomplete data.

Therefore our IPD meta-analysis provides a more accurate assessment of the benefits of macrolide treatment in adults with bronchiectasis. The most novel aspect of our study, however, is the ability to examine subgroup effects. Subgroup analyses can provide useful information for clinicians who need to decide how to use macrolides in practice, but should be treated with caution due to the risks of multiple statistical testing. The critical finding of our study is that few of the subgroup analyses showed a statistically significant interaction indicating a true difference in treatment response. Even though we pooled the results of 3 randomized trials, the total number of 341 subjects most likely still did not provide sufficient statistical power to detect all but very large subgroup effects.

With the caveat that such differences are numerical rather than statistically significant, we observed the largest relative treatment effects in older patients, with a history of 1-2 exacerbations per year, a body mass index above 30kg/m^2, a high baseline C-reactive protein, *P. aeruginosa* infection and aetiology other than idiopathic and post-infective.

The European Respiratory Society guidelines recommend consideration of macrolide treatment in patients with 3 or more exacerbations per year.[7] Our finding of a strong treatment benefit in patients with a lower frequency of exacerbations suggests that macrolides might be considered in patients with 1-2 exacerbations per year, particularly if alternative approaches to reduce exacerbations have been

unsuccessful.[7] No quality of life or lung function benefits were observed in this subgroup, however. We found no evidence that the response to macrolides was modified by the presence of *P. aeruginosa* in sputum. *P. aeruginosa* is a key pathogen in bronchiectasis as it is linked to a higher frequency of exacerbations, hospital admissions and risk of mortality.[27] Prophylactic antibiotics are widely used in these patients in view of this increased morbidity.[28] Serisier et al reported in the original BLESS trial a non-significant trend towards greater efficacy of erythromycin in patients with *P. aeruginosa*.[14] This has been interpreted and misinterpreted by some to suggest that macrolides are most effective in patients with *P. aeruginosa* or that macrolides are ineffective in patients without *P. aeruginosa*.[29,30] Our study is limited by sample size as only 61 patients out of the 341 subjects had *P. aeruginosa* with 34 of these coming from the BLESS trial. Nevertheless, it is clear that macrolides are effective in patients without *P. aeruginosa* with a statistically significant 52% reduction in the frequency of exacerbations and positive effect estimates for quality of life in this subgroup. The estimated effect in patients with *P. aeruginosa* infection was a 64% reduction in exacerbation frequency. We also observed no differential response in the small subgroup of patients with *H. influenzae* infection. Current ERS guidelines recommend that inhaled antibiotics should be considered first line for exacerbation reduction in patients with *P. aeruginosa* infection.[7] The best estimate of inhaled antibiotic efficacy in patients with bronchiectasis is an approximate 30% reduction in the frequency of exacerbations and recent randomized trials have given mixed or inconsistent results.[24,25,31,32] Our data support the use of macrolides in patients with P. aeruginosa and in the absence of head to head studies, could be an appropriate first line maintenance antibiotic in selected patients. Our results are consistent with the experience of macrolide treatment in cystic fibrosis where macrolide treatment reduces exacerbation frequency in both *P. aeruginosa* infected and uninfected patients.[33,34]

Older patients were previously identified as a subgroup more responsive to macrolides in COPD and our study suggests this may also be the case in bronchiectasis.[35] Systematic inflammation is a risk factor for exacerbation in patients with bronchiectasis and the anti-inflammatory effects of macrolides have been shown to reduce systemic inflammation including C-reactive protein.[36] The association between increased age, increased systemic inflammation and increased efficacy of macrolides is therefore biologically plausible. It is clear, however, that further studies would be required to provide sufficient statistical power to confidently identify these patients groups as more responsive to macrolide treatment.

Strengths and limitations

The strength of our study is the pooling of three high quality double blind randomized trials all of which were evaluated as being at low risk of bias. Access to IPD was comprehensive and allowed more detailed analysis than has previously been possible in aggregate meta-analysis. The three studies were conducted in different regions but showed concordant results across Europe and the Asia/Pacific region, strengthening confidence that these results will be generalizable. Our study has limitations. As outlined by the EMA guidance for interpretation of subgroup analyses of randomized controlled trials, even if a medicine is associated with benefit it will, by chance alone, appear not to work or even harm in some category or categories of patients if sufficient multiple tests are performed. We conducted 30 subgroup analyses and so at least 1-2 associations would be expected purely by chance. Results of subgroups should ideally be confirmed in future randomized studies. Many subgroups were small with very wide confidence intervals reflecting the relatively small size of the patient population overall. We were unable to evaluate some potential predictors of response such as disease severity according to multidimensional scoring systems, because some data required to calculate these scores such as radiological extent of disease were not collected in the original trial databases. We pooled two trials of azithromycin and one trial of erythromycin. Our study was not designed to evaluate any differences in efficacy between these two macrolides.

The fact that the favourable effect of macrolides now appears to extend beyond the 'traditional' frequent exacerbator should, however, not serve as a permit to unrestricted use of macrolide maintenance treatment in bronchiectasis patients. Macrolides have important adverse effects including direct side effects, population risk of antimicrobial resistance, induction of resistance in NTM, cardiovascular effects and drug-drug interactions.[8] The results of safety evaluation of the 3 trials included in our meta-analysis are extensively reported in the primary publications and subsequent meta-analyses and so were not the focus of this manuscript. This said, the trend to worse QoL in younger patients with non-frequent exacerbations (Fig 2), may very well be a reflection of more side effects in this particular subgroup, which would be consistent with the clinical experience of the authors. In each individual patient the potential benefit should be carefully balanced against the potential long term impact of macrolide treatment. Therefore, when making the decision to start macrolide maintenance treatment, international guidelines recommend that protocols for monitoring of adverse effects and subsequent response evaluation should be in place, aimed at detection of cardio-, oto- and hepatotoxicity. Recent guidelines recommend to withhold macrolide treatment in patients until active NTM infection has been excluded and in patients with evidence of a long QT-interval on ECG.

The longest trial identified in our search was 12 months and the efficacy and safety of macrolides beyond 12 months is unknown. Ideally a future randomized controlled trial should be sufficiently large to prospectively validate some of the responder subgroups identified in this meta-analysis and should have sufficiently long follow-up to establish long term efficacy and safety.

In conclusion, macrolides significantly reduce the frequency of exacerbations in bronchiectasis, prolong the time to next exacerbation and improve quality of life. This effect is evident across all patient subgroups including some patient populations such as those with *P. aeruginosa* where current guidelines do not recommend macrolides as first line.

Contributors

Study design: JDC, WB, ML, SLT, CW, JA

Literature Search: JDC, MLC, JA

Data collection: WB, LJ, MLC, NK, MLM, LDB, CW, JA

Data analysis: JDC, ML, MLC, JA

Data interpretation: JDC, WB, ML, ALT, CW, JA

Drafting the manuscript: JDC, ML, JA

Revising the manuscript and approval for submission: All authors

Conflict of interest statement

Professor Chalmers reports grants and personal fees from Glaxosmithkline, Boehringer-Ingelheim, Astrazeneca, Pfizer, Bayer Healthcare, Grifols, Napp, Aradigm corporation, and Insmed outside the submitted work. The other authors declared no conflicts of interest.

REFERENCES

1. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. *Lancet Respir Med*. February 2018. doi:10.1016/S2213-2600(18)30053-5
2. Spinou A, Fragkos KC, Lee KK, et al. The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. *Thorax*. 2016;71(8):683-694. doi:10.1136/thoraxjnl-2015-207315
3. Chalmers JD, Aliberti S, Filonenko A, et al. Characterization of the “frequent exacerbator phenotype” in bronchiectasis. *Am J Respir Crit Care Med*. 2018;197(11). doi:10.1164/rccm.201711-2202OC
4. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J*. 2017;49(6). doi:10.1183/13993003.00051-2017

5. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. *Lancet (London, England)*. 2018;392(10150):880-890. doi:10.1016/S0140-6736(18)31767-7

6. Boaventura R, Sibila O, Agusti A, Chalmers JD. Treatable traits in bronchiectasis. *Eur Respir J*. 2018;52(3). doi:10.1183/13993003.01269-2018

7. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50(3). doi:10.1183/13993003.00629-2017

8. Kelly C, Chalmers JD, Crossingham I, et al. Macrolide antibiotics for bronchiectasis. *Cochrane database Syst Rev*. 2018;3:CD012406. doi:10.1002/14651858.CD012406.pub2

9. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med*. 2013;1(3):262-274. doi:10.1016/S2213-2600(13)70038-9

10. Haworth CS, Bilton D, Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. *Respir Med*. 2014;108(10):1397-1408. doi:10.1016/j.rmed.2014.09.005

11. Chalmers JD. Macrolide resistance in Pseudomonas aeruginosa: implications for practice. *Eur Respir J*. 2017;49(5). doi:10.1183/13993003.00689-2017

12. Chang AB, Grimwood K, White A V, et al. Randomized placebo-controlled trial on azithromycin to reduce the morbidity of bronchiolitis in Indigenous Australian infants: rationale and protocol. *Trials*. 2011;12:94. doi:10.1186/1745-6215-12-94

13. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA*. 2013;309(12):1251-1259. doi:10.1001/jama.2013.1937

14. Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA*. 2013;309(12):1260-1267. doi:10.1001/jama.2013.2290

15. Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2012;380(9842):660-667. doi:10.1016/S0140-6736(12)60953-2

16. Valery PC, Morris PS, Byrnes CA, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med*. 2013;1(8):610-620. doi:10.1016/S2213-2600(13)70185-1

17. Gao Y-H, Guan W-J, Xu G, et al. Macrolide therapy in adults and children with non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. *PLoS One*. 2014;9(3):e90047. doi:10.1371/journal.pone.0090047

18. Fan L-C, Lu H-W, Wei P, Ji X-B, Liang S, Xu J-F. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. *BMC Infect Dis*. 2015;15:160. doi:10.1186/s12879-015-0872-5

19. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689-698. doi:10.1056/NEJMoa1104623

20. Schembri S, Williamson PA, Short PM, et al. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ*. 2013;346:f1235.

21. Kelly C, Evans DJ, Chalmers JD, et al. Macrolide antibiotics for non-cystic fibrosis bronchiectasis. *Cochrane Database Syst Rev*. 2016;2016(10). doi:10.1002/14651858.CD012406

22. Aliberti S, Masefield S, Polverino E, et al. Research priorities in bronchiectasis: A consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J*. 2016;48(3). doi:10.1183/13993003.01888-2015

23. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA*. 2015;313(16):1657-1665. doi:10.1001/jama.2015.3656

24. De Soyza A, Aksamit T, Bandel T-J, et al. RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur Respir J*. 2018;51(1). doi:10.1183/13993003.02052-2017

25. Aksamit T, De Soyza A, Bandel T-J, et al. RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur Respir J*. 2018;51(1). doi:10.1183/13993003.02053-2017

26. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221. doi:10.1136/bmj.c221

27. Araújo D, Shteinberg M, Aliberti S, et al. The independent contribution of Pseudomonas aeruginosa infection to long-term clinical outcomes in bronchiectasis. *Eur Respir J*. 2018;51(2). doi:10.1183/13993003.01953-2017

28. Henkle E, Aksamit TR, Barker AF, et al. Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. *Chest*. 2017;152(6):1120-1127. doi:10.1016/j.chest.2017.04.167

29. Guan W-J, Huang Y, Chen C-L, Chen R-C, Zhong N-S. Macrolides, mucoactive drugs and adherence for the management of bronchiectasis. *Eur Respir J*. 2018;51(1). doi:10.1183/13993003.01987-2017

30. Chalmers JD, Polverino E. Macrolides, mucoactive drugs and adherence for the management of bronchiectasis. *Eur Respir J*. 2018;51(1). doi:10.1183/13993003.02033-2017

31. Brodt AM, Stovold E, Zhang L. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. *Eur Respir J*. 2014;44(2):382-393. doi:10.1183/09031936.00018414

32. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med*. 2014;189(8):975-982. doi:10.1164/rccm.201312-2208OC

33. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW 3rd; Macrolide Study Group. Azithromycin in patients

with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2003 Oct 1;290(13):1749-56.

34. Saiman L, Anstead M, Mayer-Hamblett N, Lands LC, Kloster M, Hocevar-Trnka J, Goss CH, Rose LM, Burns JL, Marshall BC, Ratjen F; AZ0004 Azithromycin Study Group. Effect of azithromycin pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2010 May 5;303(17):1707-15

35. Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med*. 2014;189(12):1503-1508. doi:10.1164/rccm.201402-0207OC

36. Saleh AD, Chalmers JD, De Soyza A, et al. The heterogeneity of systemic inflammation in bronchiectasis. *Respir Med*. 2017;127. doi:10.1016/j.rmed.2017.04.009

Trials	Setting	Key inclusion criteria	Age: Mean (standard deviation)	Male:female	Macrolide drug and dose	N intervention; Control	Study duration
BAT- Altenburg 2013[13]	14 hospitals in the Netherlands 2008 to 2010	3 or more exacerbations Positive sputum culture in the year prior to baseline	59.9 (12.3) (active) vs 64.6 (9.1) (placebo)	30:53	Azithromycin 250mg daily	43 (azithromycin) vs 40 (Placebo)*	12 months (with 3 months run-out period)
BLESS- Serisier 2013[14]	Single centre, Australia 2008-2011	2 or more exacerbations Daily sputum production	61.1 (10.5) (active) vs 63.5 (9.5) (placebo)	46:71	Erythromycin ethylsuccinate 400mg twice daily	59 (erythromycin) vs 58 (placebo)	48 weeks with a 4 week washout period
EMBRACE- Wong 2012[15]	Three centres in New Zealand 2008-2009.	1 or more exacerbation in the previous year	60.9 (13.6) (active) vs 59.0 (13.3) (placebo)	43:98	Azithromycin 500mg three times per week	71 (azithromycin) vs 70 (placebo)	6 months treatment period followed by 6 months observation without treatment.

Table 1. Characteristics of the included studies

***note that 2 patients in the azithromycin group and 4 patients in the placebo group were excluded after randomization before receiving the first dose of drug. These patients were not included in the IPD analysis.**

	N (Macrolide vs placebo)	Incident rate ratio (95% CI)	p-value	p-interaction
Age groups				
<50 years	53 (27 vs 26)	0.61 (0.27-1.37)	0.23	
50-69 years	211 (110 vs 101)	0.52 (0.36-0.76)	0.001	0.18
70 years or more.	77 (36 vs 41)	0.36 (0.18-0.71)	0.003	
Sex				
male	119 (59 vs 60)	0.59 (0.35-0.99)	0.047	0.31
female	222 (114 vs 108)	0.43 (0.29-0.62)	<0.0001	
Prior exacerbation				
1-2 per year	73 (37 vs 36)	0.37 (0.16-0.88)	0.025	
3 per year	85 (48 vs 37)	0.62 (0.32-1.20)	0.072	0.86
4 or more per year	183 (88 vs 95)	0.52 (0.36-0.77)	0.001	
Smoking status				
Never	222 (115 vs 107)	0.51 (0.35-0.74)	<0.0001	
Former	112 (56 vs 56)	0.44 (0.27-0.73)	0.002	0.64
Current	7 (2 vs 5)	Not estimable	n/a	
Inhaled corticosteroid use				
Yes	223 (112 vs 111)	0.49 (0.34-0.71)	<0.0001	0.46
No	118 (61 vs 57)	0.44 (0.26- 0.75)	0.003	
Body mass index at baseline				
<21	38 (20 vs 18)	0.36 (0.13-1.02)	0.054	
21-24.9	179 (92 vs 87)	0.56 (0.37-0.84)	0.005	0.50
25-29.9	65 (36 vs 29)	0.55 (0.27-1.10)	0.093	
30 or more	59 (25 vs 34)	0.27 (0.12-0.61)	0.001	
Aetiology				
idiopathic and post-infective	267 (149 vs 118)	0.56 (0.39-0.80)	0.002	0.034
Other	74 (24 vs 50)	0.23 (0.11-0.52)	<0.0001	
Baseline C-reactive protein				
<2mg/L	98 (49 vs 49)	0.60 (0.34-1.03)	0.065	
2-5mg/L	95 (51 vs 44)	0.52 (0.30-0.92)	0.023	0.27
5.1-10mg/L	71 (36 vs 35)	0.33 (0.15-0.73)	0.006	
>10mg/L	60 (30 vs 30)	0.35 (0.17-0.76)	0.008	
Baseline FEV1				
>80% predicted	137 (64 vs 73)	0.52 (0.32-0.84)	0.008	

50-79% predicted	144 (82 vs 62)	0.43 (0.27-0.70)	0.001	0.51
<50% predicted	60 (27 vs 33)	0.55 (0.27-1.12)	0.10	
SGRQ total score				
<30	139 (72 vs 67)	0.50 (0.29-0.84)	0.008	
30-49	123 (64 vs 59)	0.45 (0.27-0.74)	0.002	0.90
50 or more	79 (37 vs 42)	0.50 (0.28-0.90)	0.022	
Pseudomonas aeruginosa				
Yes	61 (31 vs 30)	0.36 (0.18-0.72)	0.004	0.45
No	280 (142 vs 138)	0.53 (0.38-0.74)	<0.0001	

Table 2. subgroup analysis of exacerbation frequency.

	Hazard ratio (95% CI)	p-value	p-interaction
Age groups			
<50 years	0.65 (0.29-1.44)	0.29	
50-69 years	0.50 (0.35-0.72)	<0.0001	0.15
70 years or more.	0.24 (0.11-0.54)	<0.0001	
Sex			
male	0.57 (0.34-0.95)	0.030	0.22
female	0.38 (0.27-0.55)	<0.0001	
Prior exacerbation			
1-2 per year	0.40 (0.17-0.96)	0.040	
3 per year	0.47 (0.25-0.89)	0.020	0.45
4 or more per year	0.48 (0.34-0.69)	<0.0001	
Smoking status			
Never	0.49 (0.34-0.72)	<0.0001	0.34
Former	0.37 (0.22-0.58)	<0.0001	
Inhaled corticosteroid use			
Yes	0.44 (0.31-0.63)	<0.0001	0.89
No	0.46 (0.27-0.76)	0.003	
Body mass index at baseline*			
<21	0.22 (0.07-0.70)	0.010	0.24
21-24.9	0.56 (0.38-0.82)	0.003	
25-29.9	0.33 (0.17-0.67)	0.002	
30 or more	0.26 (0.11-0.59)	0.001	
Aetiology			
idiopathic and post-infective	0.53 (0.38-0.75)	<0.0001	0.11
Other	0.29 (0.15-0.57)	<0.0001	
Baseline C-reactive protein*			
<2mg/L	0.61 (0.35-1.05)	0.072	0.20
2-5mg/L	0.44 (0.26-0.76)	0.003	
5.1-10mg/L	0.27 (0.12-0.57)	0.001	

>10mg/L	0.39 (0.19-0.82)	0.013	
Baseline FEV1			
>80% predicted	0.49 (0.31-0.77)	0.002	0.86
50-79% predicted	0.37 (0.23-0.59)	<0.0001	
<50% predicted	0.54 (0.27-1.09)	0.087	
SGRQ total score			
<30	0.60 (0.37-0.98)	0.039	0.21
30-49	0.37 (0.24-0.59)	<0.0001	
50 or more	0.42 (0.23-0.77)	0.004	
Pseudomonas aeruginosa			
Yes	0.36 (0.19-0.69)	0.001	0.47
No	0.47 (0.34-0.65)	<0.001	

Table 3. Time to first exacerbation subgroup analysis

FIGURE LEGENDS

Figure 1. Flow chart of studies included in the IPD meta-analysis.

Figure 2. Forest plot showing impact of macrolide treatment on the change in quality of life using the SGRQ total score in the one-step meta-analysis. Abbreviations ICS= inhaled corticosteroid, CRP= C-reactive protein, FEV1= forced expiratory volume in 1 second, SGRQ= St.Georges Respiratory Questionnaire

Figure 3. Forest plot showing impact of macrolide treatment on the change in forced expiratory volume in 1 second in the one-step meta-analysis. Abbreviations ICS= inhaled corticosteroid, CRP= C-reactive protein, FEV1= forced expiratory volume in 1 second, SGRQ= St.Georges Respiratory Questionnaire